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Etiology of community acquired pneumonia among adult patients requiring hospitalization in Taiwan

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Summary
Background: There has not been a comprehensive multi-center study investigating the microbial profile of community acquired pneumonia (CAP) in Taiwan.
Methods: A prospective study of adult CAP patients requiring hospitalization between December 2001 and April 2002 was carried out in 13 hospitals in Taiwan.

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Cap in hospitalized adult patients

Etiology was determined based on laboratory data from blood and sputum cultures plus serology from paired serum and urine antigen detection tests.
Results: Etiology was assigned to 99 (58.9%) of the 168 patients having the most complete data for etiology determination, with mixed infection in 21 (12.5%) patients. More than half (51.8%) of the patients were >60 years and 63.7% of the patients were males. The most common etiologic agent was *Streptococcus pneumoniae* (40, 23.8%), the majority (60%, 24 cases) of which was detected by positive urine antigen test. Other common agents included *Mycoplasma pneumoniae* (24, 14.3%), *Chlamydia pneumoniae* (12, 7.1%), Influenza A virus (11, 6.5%), *Klebsiella pneumoniae* (8, 4.8%) and *Haemophilus influenzae* (8, 4.8%). The prevalence of *S. pneumoniae* and *M. pneumoniae* was highest in patients >60 years (25/87, 28.7%), and <44 years (12/59, 19%), respectively; while *K. pneumoniae* comprised a larger proportion (4/22, 18%) in the 45–59 years group.
Conclusions: *S. pneumoniae* was the most common etiology agent in adult patients hospitalized due to CAP in Taiwan and the spectrum of other major pathogens was similar to studies conducted elsewhere in the world. Empiric treatment recommendations developed in other parts of the world may be appropriately adapted for local use after taking into account local resistance profiles. Our data also support the recommendation that urine antigen test be added as an adjunct to adult CAP etiology diagnosis protocol.

Introduction

Despite the availability of potent new antimicrobials, advanced supportive therapy, and effective vaccines, community acquired pneumonia (CAP) remains a leading cause of morbidity and a significant cause of mortality worldwide, with up to 30% of patients requiring hospitalization and a mortality rate of 12% or higher in high-risk patients.[1–10] Because delayed treatment increased the risk for mortality, the management of CAP requires prompt diagnosis in order to initiate proper empiric antibiotic therapy based on the knowledge of the likely etiologic agent.[11,12] Several comprehensive CAP treatment guidelines are available in Western countries based on studies conducted in those parts of the world.[8,10,13–15]

The most commonly used and accepted laboratory methods in determining the etiologic agents of CAP to date included blood and sputum cultures, and serology.[16] Despite extensive diagnostic testing, an etiologic agent is often undetermined in as much as one-third to over half of the cases studied. In recent years, urine antigen detection assay has become an accepted adjunct to culture for determining the etiology of CAP in adults.[8,15,17,18]

In Taiwan, pneumonia was the 7th and 8th leading cause of death between 1994 and 2002. With the exception of a few reports on the role of individual CAP pathogen,[19–22] there has not been a comprehensive prospective study investigating the etiology profile of CAP in Taiwan. In a study of antibiotic usage in hospitals in Taiwan, it was found that the most common community acquired infection was pneumonia, which accounted for 24% of community acquired infection cases and a putative agent was isolated in <30% of CAP cases.[23] Thus, we initiated a prospective study of unselected adult CAP patients admitted to hospitals in Taiwan and applied results from microbiology cultures, serology and urine antigen detection assays to elucidate the etiologic agents in those patients.

Methods

Patients

Between December 1, 2001 and April 30, 2002, patients who were >16 year old, and who were admitted to internal medicine and pulmonary services in 13 hospitals throughout Taiwan with a dianosis of ''lower respiratory infection'' were examined for the possibility of CAP. The 13 hospitals included 5 medical centers, 7 regional hospitals, and 1 local hospital, with an average number of 1640, 666, and 210 beds, respectively. Patients who were enrolled must fulfill the following criteria: A chest radiograph taken within 48 h of admission revealing a new infiltrate consistent with pneumonia, and at least one of the following: fever (>38.3 °C) or chills, or hypothermia (<35.5 °C), productive cough, or abnormal white blood cell count (>11×10^9/L, or <3×10^9/L) with or without an abnormal differential. Patients who had stayed in a long-term care facility or nursing home over 21

days were excluded. The study was approved by the committee on human research at our institutes.

Data and specimen collection

Patient data was collected using a standardized questionnarie. Information collected included demogrphic characteristics, history, physical examination and laboratory results at presentation and during hospital course, additional diagnostic studies and hospital course. Results of microbiology work-up on patient sputum, blood, and pleural samples performed by the hospital were recorded. A sample of acute serum collected within 24 h of admission, a convalescent serum collected between 4 and 6 weeks after admission, and a urine sample collected within 48 h of admsision were obtained and stored frozen.

Serology and urine antigen testing

Serologic assays were used to detect IgG and IgM antibodies. Antibodies to *Chlamydia pneumoniae* and *Legionella pneumophila* (serotypes 1, 4, 6, 8 mixture); and viral agents adenovirus, influenza A, influenza B, parainfluenza 1–4, and respiratory syncytial virus; were determined using immunofluorescence assay (EUROIMMUN, Germany). Antibodies to *Mycoplasma pneumoniae* were determined by enzyme-linked immuosorbent assay (ELISA) (Savyon Diagnostics, Ashdod, Israel). Detection of *Streptococcus pneumoniae* and *L. pneumophila* antigens in urine was performed using an immunochromatographic assay (Binax NOW, Binax Inc., Maine, USA).

Assignment of etiology

Establishment of infection with specific etiologic agents included definite and probable categories following published criteria and guidelines.[1,3,8] A definite agent was assigned when (1) the isolate was cultured from blood or pleural fluid, (2) $\geqslant 4\times$ fold rise in IgG antibody titre to *L. pneumophila* (to $\geqslant$1:128), *C. pneumoniae* (to $\geqslant$1:256), or to any of the respiratory virus antigens tested, or a seroconversion of antibodies to *M. pneumoniae* based on manufacturer's criteria, (3) Detection of *L. pneumophila* antigen in urine, or (4) Detection of *S. pneumoniae* antigen in urine plus isolation of *S. pneumoniae* from purulent sputum. A probable agent was assigned when (1) A pathogen was isolated as a predominant organism from a purulent sputum in which a compatible organism was seen as a predominant organism or in at least moderate amount on Gram stain; or (2) Detection of *S. pneumoniae* antigen in urine.

Statistics

Significance of differences in frequencies and proportions was tested by the χ^2 test with Yates' correction using Epi Info 6.04 (CDC, Atlanta, GA), a database and statistical program for public health. Multiple logistic regression was used to identify risk factors for mortality using SAS 8.2 (SAS Institute Inc., Cary, NC).

Results

A total of 468 adult patients were enrolled in the study, of which 20 were excluded including 13 who stayed in a long term care facility over 21 days and 7 with no questionnaire. From these 448 patients, the etiology profile of 168 patients (37.5%) who had the most complete and definite laboratory data was analyzed in detail. The other patients either had no blood or sputum culture or lacked convalescent serum. The 168 patients included 158 who had paired serum, blood (or pleural fluid) and sputum cultures, and urine for antigen testing and 10 patients with meaningful positive blood cultures (3 *S. pneumoniae*, 3 *K. pneumoniae*, 2 *Escherichia coli*, 1 *Haemophilus influenzae*, and 1 *Staphylococcus aureus* with beta-streptococci). Patient demographic and characteristics of these 168 patients are presented in Table 1. The age distribution, sex, and proportions of patients with different characteristics of these 168 patients presented in Table 1 were very similar to all 448 patients.

Over half (51.8%) the patients were $\geqslant$60 years and a larger proportion of the patients were males (63.7%). A total of 53.6% of the patients had at least one comorbidity present, and 32.2% had two or more comorbidities (data not shown). The most common radiography finding was in the right lower lobe (51.1%) with 39.7% of patients having multilobar infiltration. Very few patients reported having been vaccinated for *H. influenzae* (2, 1.2%), pneumococci (2, 1.2%), and influenza (9, 5.4%) (data not shown). Only less than half (44.6%) of the patients knew for certain they did not receive antibiotics prior to admission.

Using the definite and probable diagnosis criteria, 121 etiologic agents (84 in definite and 37 in probable category) were assigned to 99 (58.9%) of the 168 patients (Table 2). Combining definite and probable agents, the most common pathogen

Table 1 Demographic and characteristics of 168 hospitalized adult CAP patients in Taiwan.

Variable	No. of patients (%)*
Age, mean+SD (range)	56.1+22.8 years (17–99 years)
17–44 years	59 (35.1)
45–59 years	22 (13.1)
⩾60 years	87 (51.8)
Male	107 (63.7)
Comorbidity present	90 (53.6)
Pulmonary	35 (20.8)
Hypertension	37 (22.0)
Cardiovascular	34 (20.2)
Diabetes mellitus	21 (12.5)
Renal	21 (12.5)
Neurologic	14 (8.3)
Neoplastic	9 (5.4)
Hepatic	8 (4.8)
Immunosuppression	2 (1.2)
Clinical presentation on admission	
Cough	109 (64.9)
Fever (38.2 °C) or chills	134 (79.8)
Hypothermia	4 (2.4)
Leukocytosis	91 (54.2)
Leukopenia	4 (2.4)
Abnormal differential	21 (12.5)
Radiography presentations†	
Right lower lobe	86 (51.1)
Left lower lobe	65 (38.7)
Right middle lobe	41 (24.4)
Right upper lobe	22 (13.1)
Left upper lobe	14 (8.3)
Multi-lobar involvement	67 (39.7)
Antibiotic use prior to admission	
No antibiotic used	75 (44.6)
Unknown or unreliable	66 (39.3)
Antibiotic used	27 (16.1)
Mortality	14 (8.3)

*Data are number (percentage) of patient for each variable except patient age.

†Location of radiography finding: data represent single and multi-lobar infiltration combined.

identified was *S. pneumoniae* (40, 23.8%), followed by *M. pneumoniae* (24, 14.3%), *C. pneumoniae* (12, 6.5%), Influenza A (11, 6.5%), *H. influenzae* (8, 4.8%), and *K. pneumoniae* (8, 4.8%). Coinfection with more than one etiologic agent was found in 21 (12.5%) patients. The most common coinfection combination was *S. pneumoniae* with another agent (12, 7.1%), of which 6 (3.6%) were with *M. pneumoniae*. The etiology of 69 (41.1%) patients was unknown. The rate of etiology unknown was not significantly different ($P>0.05$) among the patients having no prior antibiotic use (48.0%, 36/75), and uncertain antibiotic use history (33.3%, 22/66), and antibiotic used group (40.7%, 11/27).

Of the 40 *S. pneumoniae* cases in the present study, 12 were in the definite category, 5 of which had positive blood cultures, 4 of them had positive urine antigen results also; the other 7 cases had *S. pneumoniae* in purulent sputum cultures and positive urine antigen tests. Of the other 28 *S. pneumoniae* cases in the probable category, 4 had positive sputum culture with compatible Gram stain but negative urine antigen test; 24 had negative sputum culture but positive urine antigen test. Only one of the 24 culture-negative, urine antigen-positive patients had received pneumoncoccal vaccine 8 months prior to hospitalization; and 14 patients either had received antibiotics or were not certain about antibiotic usage.

Patients were also divided into three groups by age, 17–44 years (59, 35.1%), 45–59 years (22, 13.1%), ⩾60 years (87, 51.8%), to look for pathogens more commonly associated with an age group. The most common etiologic agent in the younger (17–44 years) group was *M. pneumoniae* (19.0%), while in the older (⩾60 years) group the most common pathogen was *S. pneumoniae* (28.7%). *K. pneumoniae* comprised significantly larger proportion in the 45–59 years group compared to the other two age groups (18.2% vs. 1.7% and 3.4%; $P<0.01$). Patients in the 45–59 years group also had a smaller percentage of etiology unknown (18.2% vs. 38.9% and 48.3%, $P<0.05$) (Table 3).

The mortality rate was 8.3% (14/168). Of the 14 patients who died, etiologic agents was identified in 11 patients, including 5 *S. pneumoniae* (1 with *M. pneumoniae*), 3 *K. pneumoniae*, 1 *E. coli*, 1 *Staphylococcus aureus* with beta-streptococci, and 1 *C. pneumoniae*; 4 of whom were bacteremic (*S. pneumoniae*, *K. pneumoniae*, *E. coli*, and *S. aureus* with beta-streptococci). The mean age of the patients who died was 75.0 years compared to 55.0 years in the patients who survived. Univariate analysis showed that age (Odds ratio (OR), 8.67, 95% confidence interval (CI), 1.88–40.06; $P<0.01$), comorbidities (OR, 1.75; CI 1.18 –2.58; $P<0.01$), and bacteremia (OR 5.56; CI, 1.63–18.88; $P<0.01$) were risk factors associated with mortality. Multiple regression analysis also showed that age (OR 1.75; CI 1.164—2.633; $P<0.01$) and bacteremia (OR 5.55; CI 1.53–20.12; $P<0.01$) were risk factors associated with mortality.

Discussion

Many studies conducted in North America, Europe, and other Asian countries have found *S. pneumonia*e

Table 2 Etiologic agents of 168 adult community acquired pneumonia patients requiring hospitalization in Taiwan.

Etiologic agent	Diagnostic category, No. (%)*		Total
	Definite	Probable	
Streptococcus pneumoniae	12 (7.1)	28 (16.1)	40 (23.8)
Haemophilus influenzae	2 (1.2)	6 (3.6)	8 (4.8)
Staphylococcus aureus	3 (1.8)	0	3 (1.8)
Beta-Streptococci	2 (1.2)	0	2 (1.2)
Gram-negative bacilli			
Klebsiella pneumoniae	5 (3.0)	3 (1.8)	8 (4.8)
Escherichia coli	3 (1.8)	0	3 (1.8)
Mycoplasma pneumoniae	24 (14.3)	‡	24 (14.3)
Chlamydia pneumoniae	12 (7.1)	‡	12 (7.1)
Legionella pneumophila	2 (1.2)	‡	2 (1.2)
Influenza A virus	11 (6.5)	‡	11 (6.5)
Respiratory syncytial virus	2 (1.2)	‡	2 (1.2)
Adenovirus	2 (1.2)	‡	2 (1.2)
Parainfluenza virus	2 (1.2)	‡	2 (1.2)
Mycobacteria tuberculosis	2 (1.2)	‡	2 (1.2)
Total no. of patients (%)†	73 (43.5)	36 (21.4)	99 (58.9)†

*Values for mixed infections are included for each of the infecting organisms.
†Due to the presence of multiple organisms in some patients, the total number of patients is lower than the sum of patients for each agent.
‡Diagnostic category not available for specific pathogen.

Table 3 Etiologic agents of 168 adult community acquired pneumonia patients requiring hospitalization in Taiwan by age group.

Etiologic agent, (Definite and probable combined)	No. (%) of patients, by age group			
	17–44 years ($n = 59$)	45–59 years ($n = 22$)	$>= 60$ years ($n = 87$)	P*
Streptococcus pneumoniae	11 (17.2)	4 (18.2)	25 (28.7)	NS
Haemophilus influenzae	5 (8.6)	1 (4.5)	2 (2.3)	NS
Staphylococcus aureus	2 (3.4)	0	1 (1.1)	NS
Beta-Streptococci	0	0	2 (2.3)	NS
Gram-negative bacilli				
Klebsiella pneumoniae	1 (1.7)	4 (18.2)	3 (3.4)	<0.01
E. coli	0	0	3 (3.4)	NS
Mycoplasma pneumoniae	12 (19.0)	4 (18.2)	8 (9.2)	NS
Chlamydia pneumoniae	3 (5.1)	3 (13.6)	6 (6.9)	NS
Legionella pneumophila	1 (3.3)	1 (4.5)	0	NS
Influenza A virus	5 (8.6)	2 (9.0)	4 (4.6)	NS
Respiratory syncytial virus	1 (1.2)	0	1 (1.1)	NS
Adenovirus	2 (6.6)	0	0	NS
Parainfluenza virus	1 (3.3)	1 (4.5)	0	NS
Mycobacteria tuberculosis	0	0	2 (2.3)	NS
No of patients with:				
Single infection	28 (47.5)	16 (72.7)	34 (39.1)	0.02
Mixed infection	8 (13.6)	2 (9.1)	11 (12.6)	NS
Etiologic agent not identified	23 (38.9)	4 (18.2)	42 (48.3)	0.03

*χ^2 analysis of proportions in the three strata; NS, not significant (>0.05).

Table 4 Comparison of the proportions of etiology agents of hospitalized adult CAP patients in Taiwan and other countries.

Condition and Etiologic agent	Taiwan ($n = 168$)	UK ($n = 267$)	USA ($n = 2776$)	Finland ($n = 135$)	Netherlands ($n = 334$)	Israel ($n = 346$)	Thailand ($n = 147$)	Japan ($n = 326$)
Reference no.		6	3	5	1	2	7	4
Month/year started	Dec 2001	Oct 1998	1991	Sept 1981	Jan 1991	Nov 1991	Sept 1998	July 1994
Length of study	5 months	1 year	1 year	1 year	2 years 3 months	1 year	2 years 7 months	3 year
Age, mean (range), years	56.1 (17–99)	65.4 (18–97)	—* (>18)	— (15–92)	— (17–92)	49.3 (17–94)	58.9 (−)	65.2 (18–93)
Male	63.7%	51%	51.4%	—	58.4%	54%	67.3%	72%
Etiologic agent								
S. pneumoniae	24%	48%	13%	47%	27%	43%	22%	23%
H. influenzae	5%	7%	7%	4%	8%	5.5%	3%	7%
M. pneumoniae	14%	3%	32.5%	5%	6%	29%	7%	5%
C. pneumoniae	7%	13%	9%	16%	3%	18%	16%	3%
Enterobacteriaceae	6.5%	1%	3%		3%		12%	4%
S. aureus	2%	1.5%	%		1%		3%	3%
L. pneumophila	1%	3%	3%		2%	16%	5%	<1%
Viruses	10%	23%	12%	10%	8%	10%	—	4%
M. tuberculosis	1%		1%			2%		1.5%
Mixed infection	12.5%	28%	—	17%	10%	39%	6%	4%
Mortality	8.3%	15%	9%	—	8%	—	16% –53%	6%
Etiology unknown	41%	25%	60%	33%	45%	19%	29%	39%

*—, No data.

to be the most common etiologic agent in adult CAP patients, followed by atypical pathogens *M. pneumoniae* and *C. pneumoniae*, *H. influenzae,* and viruses.[1–7] Other pathogens such as *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *S. aureus*, *L. pneumophila*, and *M. tuberculosis* also accounted for various percentages as CAP agents. The rank orders of these etiologic agents varied depending on laboratory testing methods, diagnostic criteria and categories. We also found *S. pneumoniae* (23.8%) to be the most common identifiable etiologic agent of adult CAP patients admitted to hospitals in Taiwan, followed by *M. pneumoniae* (14.3%), *C. pneumoniae* (7.1%). The contribution of these 3 agents in CAP varied widely in other studies, ranging between 13–48% (*S. pneumoniae)*, 3%–32.5% (*M. pneumoniae*), and 3–18% (*C. pneumoniae*).[1–7] A comparison of patient demographics and etiology profiles from the present study with several studies conducted in other countries is presented in Table 4.

Despite applying blood and sputum microbiology cultures, paired serum serology, and urine antigen tests, the etiology was identified in only 58.9% of the patients in the present study. Two major CAP management guidelines consider the pneumoncoccal urinary antigen assay as a recommended and acceptable diagnostic test to augment the standard microbiology cultures for adult cases,[8,15] Out of the 40 *S. pneumoniae* cases identified in the present study, 24 were due to a positive urine antigen test alone. Studies have shown excessive and inappropriate antibiotic use in Taiwan outpatients, especially in respiratory infections.[23,24] In a study of patients seen at the emergency department of a major medical center in Taiwan, antimicrobial activity in urine was found in half of patients admitted to the hospital, which resulted in masked diagnosis of infectious diseases.[25] Although the rates of etiology unknown among the patients having received prior antibiotics and those having no prior antibiotic use were similar in the present study, it is still possible that prior antimicrobial use affected the recovery of CAP bacterial pathogens in routine microbiology cultures, which contributed both to the etiology unknown cases (41.1%) and the *S. pneumoniae* cases being diagnosed by urine antigen alone.

In the present study, coinfection was found in 12.5% of patients. Mixed infections involving multiple bacterial pathogens or a combination of bacterial and viral pathogen is not an uncommon finding in CAP although rates of coinfection varied (4–39%, Table 4). Three studies conducted in Western countries also determined antibodies to different *S. pneumoniae* antigens in addition to determining antibodies to atypical bacterial and viral agents, and employing urine antigen test.[2,5,6] These studies found higher mixed infection rates (17–39%), with *S. pneumoniae* mixed with *M. pneumoniae*, or *C. pneumoniae* mixed with another pathogen being the most common findings. Even though we did not test for antibodies to *S. pneumoniae* antigens, we still found *S. pneumoniae* to be the most common pathogen mixed with other pathogens in our coinfection cases.

There were more males than females in hospitalized adult CAP patients in the studies presented in Table 4, but the proportion was higher in Asian countries (67.3% in Thailand, 72% in Japan) than Western countries (51–58%).[1–7] We also found a higher proportion (63.7%) of patients being males in our study. The reason for this is unknown but it may be related to smoking as higher percentage of males are smoker in Taiwan, Thailand and Japan where smoking prevalence was 40–60% and $<10\%$ for males and females, respectively; compared to smoking prevalence of 20–30% for both males and females in Western countries such as US and UK.[26]

One limitation of the present investigation is that other studies have found seasonal variations in CAP with higher incidences for all age groups in the winter and spring.[2,5,6] Because our study was conducted over a 5-month period from December to April, we were not able to determine seasonal variations in etiology profiles. It is possible that the proportion of each of the etiologic agent in the warmer months could be different since there was a report of 13 severe CAP cases due to *Acinetobacter baumannii* in a Taiwan hospital, 11 (85%) of which were found between April and October.[19] Another limitation is that even though we tested patient urines for *L. pneumophila* antigen, we did not culture for *Legionella* spp., thus the role of *Legionella* spp. in the present study may be underestimated.

This is the first report of a national multi-center prospective study of the etiology of adult patients with CAP requiring hospitalization in Taiwan. Our results indicated that despite differences in climate temperate, the etiology profile in Taiwan is similar to that of Western and other Asian countries, with *S. pneumoniae* being the most common pathogen, followed by *M. pneumoniae* and *C. pneumoniae*; albeit differences in the proportions of each etiologic agent exist. Gram-negative bacilli, especially *K. pneumoniae*, also play an important role in hospitalized CAP patients in Taiwan, especially in the 45–59 years age group. Our results also supports the recommendation that urine antigen test be added to the diagnostic protocol for adult CAP patients. High rates of resistance in *S. pneumoniae* and other bacterial

pathogens in Taiwan have been reported.[27–29] Empiric treatment guidelines developed in other parts of the world may be appropriately adapted for use in Taiwan after taking into account local resistance trends.

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